PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Manufacture of Steroid Compounds

We, SCHERING AKTIENGESELLSCHAFT, a body corporate organised according to the laws of Germany, of 170/172 Müllerstrasse, Berlin N. 65, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the manufacture of steroid compounds.

It is known that the 17α-hydroxyl group of such steroids as also contain an acetyl group on the 17-carbon atom, can only be esterified by the application of stringent reaction conditions. However, this esterification can be carried out quite smoothly in the case of those aliphatic carboxylic acids of generally good reactivity, when the anhydrides or acid chlorides thereof, the latter advantageously in the form of a solution in the corresponding acid, are reacted upon the specified 17α-hydroxy steroids in the presence of strongly active esterification catalysts such as *p*-toluene sulphonic acid. This method also fails, however, when attempts are made to esterify the said steroids with less strongly reactive acids such as β-cyclopentyl-propionic acid. Thus even when the time of reaction of β-cyclopentyl-propionyl chloride, in the presence of β-cyclopentyl-propionic acid as solvent, is extended to 8 days, using up to 1·1 mol equivalents of *p*-toluene sulphonic acid as esterifying catalyst, neither at 20° nor at 37°C can any significant esterification of 17α-hydroxy-pregn-5-en-3β-ol-20-one-3 acetate in 17-position be effected.

The present invention is based on the observation that the esterification of the 17*α*-hydroxyl group with carboxylic acids can be caused to take place in the case of steroids containing an acetyl group on the 17-carbon atom, when the acid is reacted upon the specified steroids in the anhydrous condition in the presence of trifluoracetic anhydride at somewhat elevated temperatures, preferably at 80 — 90°C.

The introduction of the β-cyclopentyl-propionyl residue into the 17α-hydroxyl group may thus be caused to take place in a surprisingly short time and with an excellent yield.

Steric rearrangements of the steroid in the region of the cyclopentane ring do not occur (cf. especially Example 2 below). Even any keto group also present in the steroid molecule, which as is known tend to be converted into enol esters when *p*-toluene sulphonic acid is used as esterification catalyst, remain unattacked in the case of the esterification method of this invention.

New steroid esters produced by the present process are intended for use as medicaments or as intermediate products for the manufacture thereof. The β-cyclopentyl-propionyl compounds are distinguished from the β-cyclopentyl-propionyl compounds of other steroids, which have been known for some time, by a comparatively surprisingly good solubility in oleaginous solvents.

The following examples illustrate the invention:

Example 1

5 Grams of 17α-hydroxy-pregn-5-en-3-ol-20-one-3 acetate are introduced into a mixture having a temperature of 80°C and consisting of 10 cc of β-cyclopentyl-propionic acid and 5 cc of trifluoracetic anhydride. The homogeneous reaction mixture is maintained for 45 minutes at the specified temperature and then, after cooling, poured into water. The oil which is thereby precipitated is taken up in ether, washed with dilute caustic soda solution for removal of the excess of acid, dried over sodium sulphate and freed from ether by evaporation under vacuum. The oily residue is caused to crystallise by means of pentane and recrystallised from isopropyl ether.

[*Price 3s. 6d.*]

Price 25p

Yield 5·53 grams, equals 83·7% of the theoretical, of 17α-hydroxy-pregnenolone-3-acetate-17-β-cyclopentyl-propionate, m.p. 137·138·5°C.

Example 2

1 Gram of 17α-hydroxyprogesterone, 4 cc of caproic acid and 1 cc of trifluoracetic anhydride are reacted as described in Example 1 and worked up. Yield 860 mg, equals 66·5% of the theoretical, of 17α-hydroxy-progesterone caproate of m.p. 120-121°C.

This product is identical with identifiable material prepared by the known process using caproic acid anhydride in the presence of *p*-toluene sulphonic acid. This proves that, in spite of the very energetic reaction conditions, no steric rearrangement has taken place in the region of the cyclopentaone ring of the steroid nucleus.

Example 3

1 Gram of 17α-hydroxyprogesterone is added to a mixture having a temperature of 80°C. and consisting of 4 cc of β-cyclopentyl-propionic acid and 1 cc of trifluoracetic anhydride and reaction effected and working up carried out in an analogous manner to that described in Example 1. Yield of 17α-hydroxy - progesterone - 17 - β - cyclopentyl-propionate 980 mg, equals 71% of the theoretical. M.p. 128—131°C., $[\alpha]_D^{22}$ + 53·6° (c=1; in chloroform); λ max 241 mμ; ε 17 000 (Methanol).

WHAT WE CLAIM IS:—

1. A process for the manufacture of steroid compounds by the introduction of residues of carboxylic acids into the 17α-hydroxyl group of such steroids as contain on the 17-carbon atom an acetyl group in addition to the hydroxyl group, wherein a carboxylic acid is reacted in the anhydrous condition in the presence of trifluoracetic anhydride, at somewhat elevated temperature, preferably at 80—90°C, upon a steroid as specified.

2. A process for the manufacture of 17α-hydroxy-pregn-5-en-3-ol-20-one-3-acetate-17-β-cyclopentyl-propionate, wherein anhydrous β-cyclopentyl-propionic acid is reacted upon 17α-hydroxy-pregn-5-en-3-ol-20-one-3 acetate in the presence of trifluoracetic anhydride at somewhat elevated temperature, preferably at 80—90°C.

3. A process for the manufacture of 17α-hydroxy-pregn-5-en-3-ol-20-one-3-acetate-17-β-cyclopentyl-propionate, conducted substantially as described in Example 1 or 3 herein.

4. A process as claimed in Claim 1, conducted substantially as described in Example 2 herein.

5. 17α-Hydroxy-pregn-5-en-3-ol-20-one-3-acetate-17-β-cyclopentyl-propionate.

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